"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. **No. NO1-DC-4-0005**
Progress Report #2

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Overview of PABI patient results

Five patients have now received the penetrating auditory brainstem implant (PABI). After resection of vestibular schwannomas due to Type II neurofibromatosis, they were implanted with an array of 14 macro electrodes that resides in the lateral recess, over the cochlear nucleus, and an array of 8 activated iridium microelectrodes that penetrate into the nucleus. Penetrating electrodes have produced auditory percepts in three of the five patients and produced neither auditory nor non-auditory effects in two patients. Radiological evidence indicates that the penetrating electrode assembly was dislodged from its implanted location in PABI#4. Radiological results from PABI#5 are pending. No PABI patient is receiving significant open-set speech recognition, even though PABI #1 and #2 have more than one year of experience. The two PABI patients who receive auditory percepts from multiple penetrating electrodes prefer the sound of a "mixed" electrode map, which is comprised of both surface and penetrating electrodes.

Threshold levels and stability

Thresholds and dynamic range are measured each time patients return for follow-up, at approximately three month intervals. Figures 1-5 show all threshold measures from all PABI patients. Each figure shows thresholds for surface electrodes (open symbols) and for penetrating electrodes (filled symbols). Open circles show data from electrodes along one side of the surface array, while open triangles present data from electrodes along the other edge of the surface array. For each electrode the two symbols connected by a vertical solid line show the threshold and most-comfortable loudness level for that electrode. Measurements over time are slightly offset to the right; each successive pair of points indicate threshold and MCL measures at successive 3-

Fig 1: PABI #1 Threshold and MCL

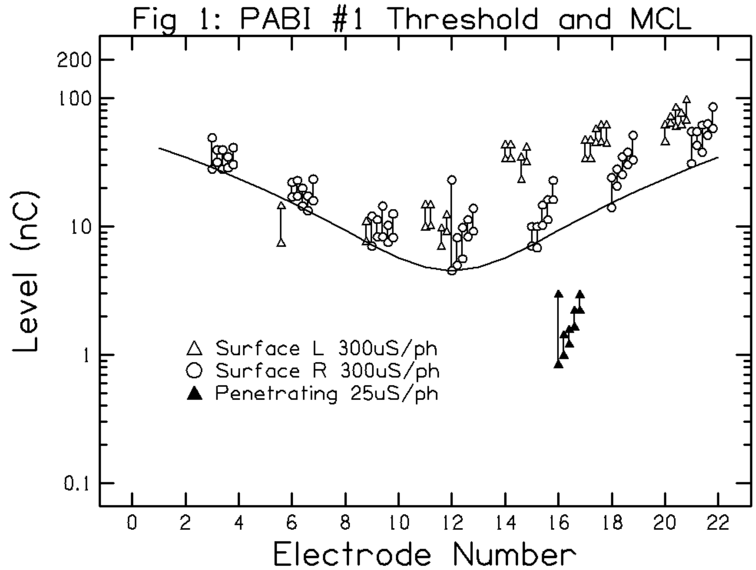
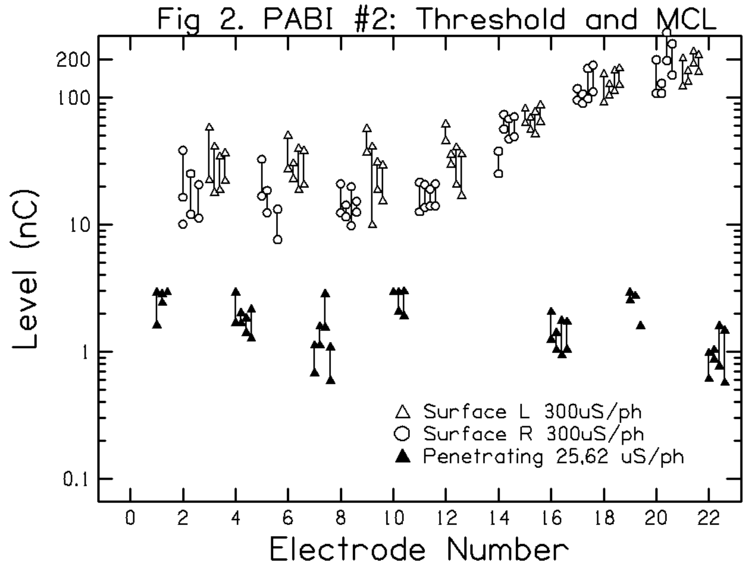
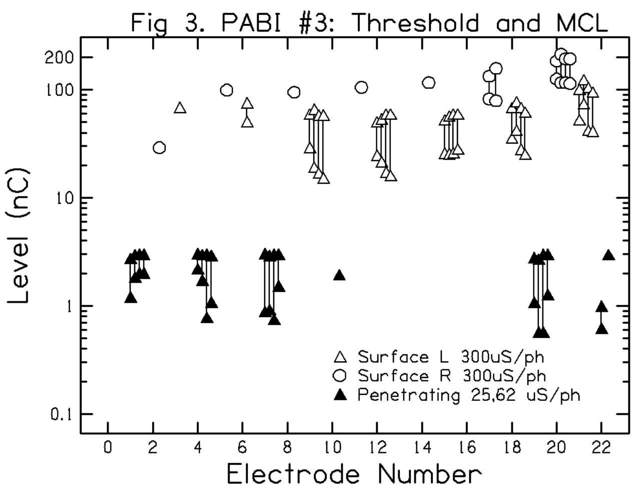
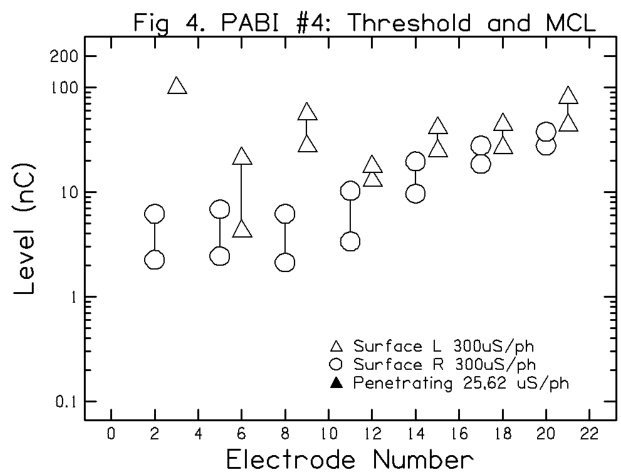


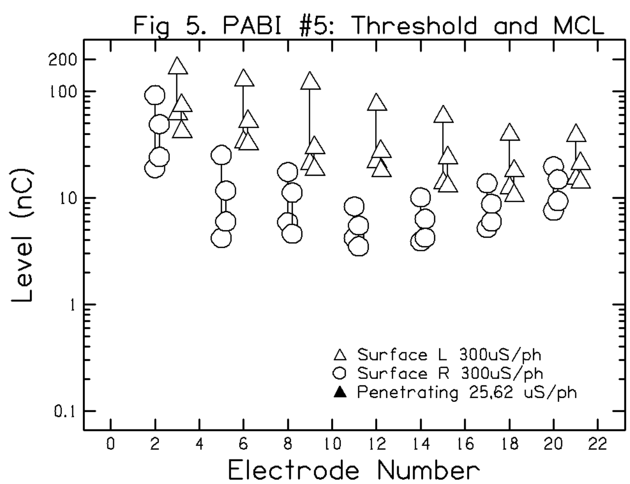
Fig 2. PABI #2: Threshold and MCL



month intervals. Note that some electrodes show a trend to increased threshold over time and others show stability or a decrease in threshold over time. There is no clear pattern of a shift that might indicate neural damage or a shift in location on most electrodes. In most cases the shift in thresholds and MCLs are smaller than the test-retest variability. Although PABI#4 and PABI#5 did not have any penetrating electrode that produced auditory sensations, the threshold levels on their surface electrodes were quite low (2-5 nC), indicating that the surface array was in nearly an optimal position. In most of the patients lower thresholds were observed on one side of the surface array than the other, indicating that one side of the electrode array was further from stimulable tissue. The implication is that this difference is either due to a tilted electrode with respect to the CN axis or to lateral displacement of the electrode array relative to the CN.





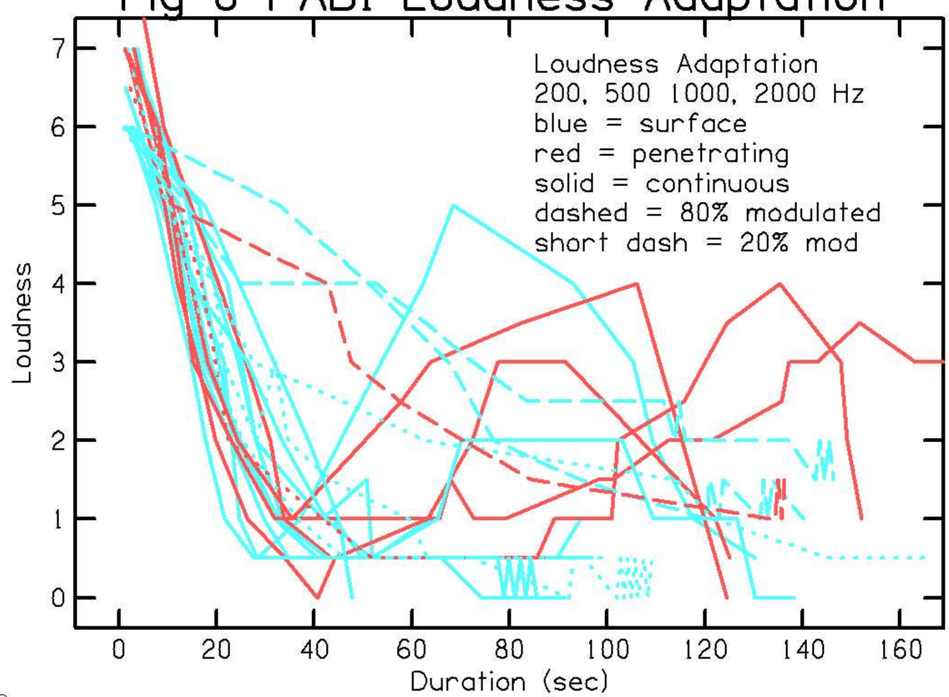


Adaptation

Adaptation was measured as an indication of SIDNE (stimulus induced depression of neural excitability. SIDNE is defined as a persisting depression of neuronal excitability (lasting many minutes to several days), as distinguished from brief adaptation. SIDNE was observed in animal models of PABI stimulation when the stimulation rates were higher than 300 pps, and was sustained for many minutes. Assuming that SIDNE might be a precursor of neural damage, we wanted to be cautious about measurements to assess SIDNE. We presented a continuous pulse train at a given stimulation rate and asked the patient to indicate the loudness (on an arbitrary scale of 0-10) every few seconds. They were familiar with this scale from routine testing, and typically assigned numbers of 5-6 as comfortably loud. We typically started with a stimulus that produced a sound that was rated 6-8 in loudness at a low stimulation rate (100-200 pps). We tracked the listener's subjective loudness levels over time to see if the loudness adapted. If so, we presented modulated pulse trains to see if modulation reduced the adaptation produced by a steady pulse train. If stimulation produced loudness adaptation we then measured thresholds again immediately after turning off the pulse train that produced the adaptation. If SIDNE were occurring we would expect that threshold levels would be elevated for some time following adaptation. We tested for SIDNE in patients PABI 1, 2, and 3. In all cases continuous stimulation produced adaptation of varying degrees. Modulation reduced the adaptation or lengthened the time over which adaptation occurred. However, in all cases thresholds were unaffected, even when measured immediately after the termination of the adaptation-inducing stimulus. We conclude that within the parameters tested we saw no signs of SIDNE. The adaptation observed was similar in degree and time course to that observed in cochlear implants and in patients with the surface-electrode ABIs.

PABI#1 was presented with pulse rates of 250, 500, 1000, and 2000 pps on a surface electrode and her one penetrating electrode. On the surface electrode there was no noticeable adaptation; sounds that were 5-6 in loudness

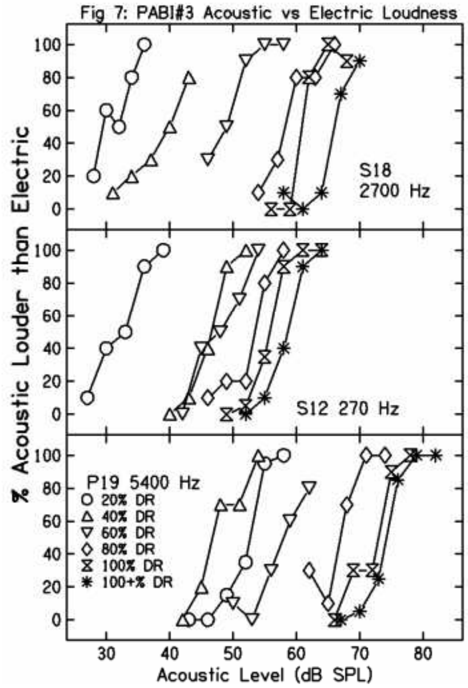
Fig 6 PABI Loudness Adaptation



were sustained at that loudness for at least 20 sec. On the penetrating electrode loudness levels of 5-6 could not be achieved due to the 3 nC charge limit. The 250 pps stimulation started at 3-4 loud and showed no adaptation over 20 sec. 500 pps stimulation, which produced a 4-5 loudness also showed no adaptation over 20 sec. However, 1000 and 2000 pps stimulation produced modest adaptation. These stimuli were only judged to be 2-3 loud initially and decreased over several seconds to a loudness value of 1. Thresholds measured immediately after adaptation showed no elevation. Loudness judgments also recovered almost instantaneously. When the continuous stimulation produced adaptation in loudness so that the sensation level decreased to 0-2 in loudness magnitude, the stimulation was terminated and then restarted within 1 sec. After only a 1 sec delay loudness had recovered fully to its pre-adaptation level.

PABI#2 was tested on several surface and several penetrating electrodes for SIDNE for continuous stimulation at rates of 250, 500, 1000, and 2000 pps. The results are shown in Fig 6 as loudness over time. The test stimulus was present for the entire duration of each plot. Almost every condition (electrode, stimulation rate, modulation) produced the same adaptation profile. Loudness decreased from 6-7 at the start to 0-2 loud after 20-40 sec. There was no clear difference in adaptation between surface and penetrating electrodes. In the presence of continuous stimulation we sometimes observed a rebound in loudness, where after declining to near threshold loudness, the loudness increased from 60-100 sec up to 3-4 loud, and then declined again. Stimuli that were modulated at 20% modulation depth produced similar adaptation time courses as unmodulated stimuli. Stimuli modulated at 80% depth produced slower adaptation time trajectory than unmodulated stimuli. Rather than decaying in loudness over 20-40 sec, stimuli with 80% modulation depth showed adaptation over a time course of 100 sec or more.

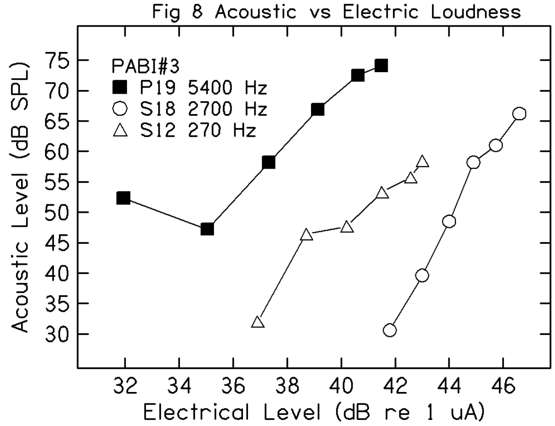
Fig 7: PABI#3 Acoustic vs Electric Loudness



Loudness

PABI # 3 has almost normal hearing remaining in the ear contralateral to the brain stem implant (although a vestibular schwannoma on that side will eventually eliminate the residual acoustic hearing). We were able to match the loudness of his electrically stimulated PABI device with calibrated acoustic stimuli presented to the other ear. Several electrical levels were selected on one penetrating (P19) and two surface electrodes (S12 and S18) that

Fig 8 Acoustic vs Electric Loudness



spanned the dynamic range from soft to loud. Acoustic stimuli were presented from 25 to 80 dB SPL at the acoustic frequency that was matched in pitch to the electrode. Within a testing block electrical stimulation was presented to only one electrode. Within each block two stimuli were selected at random for each trial – one electrical and one acoustic. The listener's task was to select which of the two sounds was louder. Each pairing was presented 10 times in random order. We then compiled a matrix of electric vs acoustic levels. Each row in the matrix specifies a method of constant stimuli psychometric function for a given electrical level. The results are presented in Figure 7. Sigmoidal functions were fit to these curves and the point of subjective equality for loudness was determined for each electrical stimulus. Figure 8 presents the loudness growth functions for the three electrodes in terms of equivalent acoustic loudness. Note that the curves are approximately linear in dB uA vs acoustic dB – this is not consistent with earlier loudness matching results and loudness models in cochlear implants and ABIs (Zeng and Shannon, 1992,1994). We will analyze these data further to see if this apparent discrepancy can be resolved.

Modulation Detection Threshold (MDT)

MDT as a function of Level. Fu (2002) showed a dramatic correlation between modulation detection and speech recognition in cochlear implant listeners. The correlation was strongest when the average modulation detection across the dynamic range was used, rather than the best modulation thresholds, or the modulation sensitivity at a fixed level or fixed loudness. Fu suggested that modulation detection was important for both soft and loud components of speech so that modulation sensitivity at any one level was not an adequate measure for speech. We measured modulation sensitivity for the PABI patients for both surface electrodes and penetrating electrodes as a function of level. Figure 9 shows modulation thresholds in dB re 100% modulation (20 Log m) as a function of level. Note that there is no apparent difference between modulation sensitivity on surface or penetrating electrodes. Note that all PABI patients had relatively poor modulation sensitivity – requiring more than 10%

Fig 9: 10-20 Hz Modulation Detection

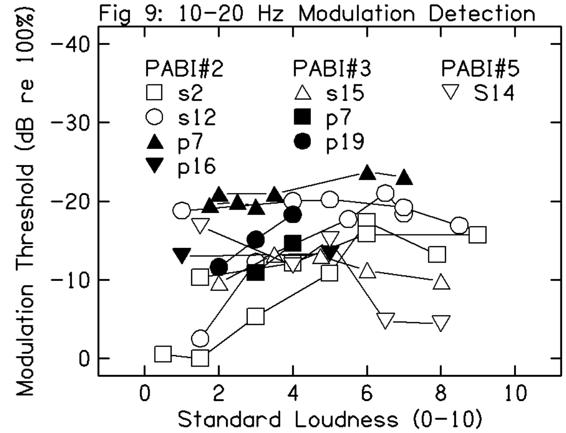


Fig 10: Avg Modulation Thresh vs Vowels

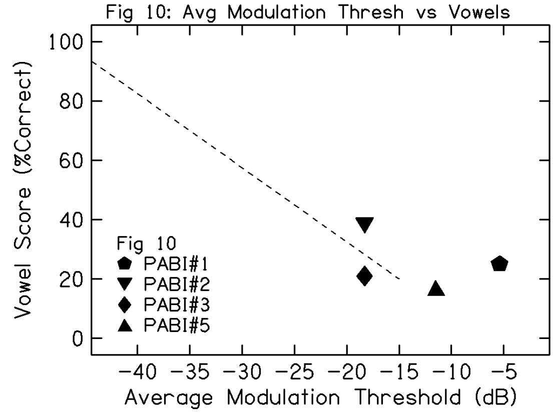
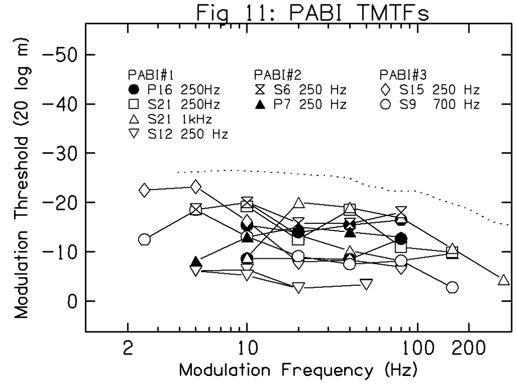


Fig 11: PABI TMTFs



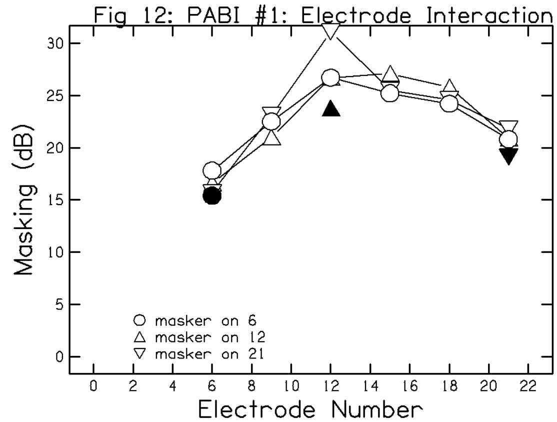
modulation for detection. Normal hearing listeners can detect modulation of 3-4% and the CI listeners with the best speech recognition in the Fu study could detect less than 1% modulation. Figure 10 shows the average modulation detection thresholds from PABI patients plotted against vowel recognition. The dashed line in the figure is from the Fu (2002) study. Note that all PABI patients fall near the line, but have poor speech recognition and poor modulation sensitivity. We will continue to monitor modulation sensitivity over time to see if there might be improvements in speech recognition and modulation sensitivity with practice and experience.

<u>MDT as a function of Modulation Frequency.</u> Speech consists of sound production that varies over time. Vowels are relatively steady-state over 100 ms or longer, while consonants can be long or short. Transitions between vowels and consonants can be characterized as modulation in amplitude or frequency at rates of 2-16 Hz. As a psychophysical index of the ability to detect modulation in time we measured the modulation transfer function (MTF) in PABI patients. The MTF measures the modulation detection threshold as a function of modulation frequency. In normal hearing listeners the MTF is low-pass in shape, showing best modulation sensitivity at low modulation frequencies and requiring progressively more modulation depth for detection as modulation frequency increases above about 60 Hz (Viemeister, 1979). Figure 11 presents MTFs for PABI patients. Note that the functions are mostly low-pass in shape, but some have a significantly lower cut-off frequency than normal hearing listeners. Overall, modulation sensitivity is relatively poor, with most measures between –10 and –20 dB, which is 10-30% modulation.

Electrode Interaction

One goal of penetrating electrode was to increase the selectivity of stimulation of each electrode. It was hypothesized that the cause or the limited speech recognition in listeners with surface electrode ABIs was that the surface electrodes were not in close proximity to the tonotopic strata of the human cochlear nucleus. By the time the stimulation activated auditory neurons it was thought that the activated sector of nerves was broad, and that stimulation of adjacent electrodes would produce interactions because they were activating highly overlapping neural populations. Penetrating electrodes in contrast are in intimate contact with auditory neurons and have very low activation thresholds and so each penetrating electrode should activate a unique sub-population of auditory neurons in the CN. Electrode interaction was assessed with forward masking. A 300 ms masking stimulus was delivered to an electrode at a level that produced a comfortable to moderately loud sensation (indicated by a filled symbol in Figs 12-15). Following the offset of

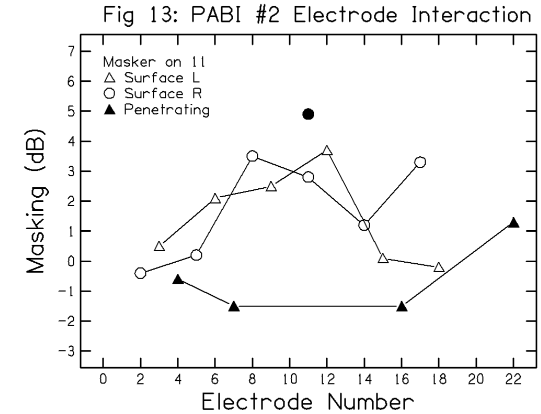
Fig 12: PABI #1: Electrode Interaction



the masker a short (20 ms) probe stimulus was presented to another electrode in the array. If the masker and probe electrode activated overlapping neural populations there should be interference and the threshold for the probe stimulus should be elevated. If the masker and probe stimulate distinct and non-overlapping neural populations the probe threshold should be similar to its threshold without the masker, i.e. no threshold elevation should be observed. We placed a masker on an electrode in the middle of the surface array and measured the threshold elevation on all other electrodes. Results are presented in Figs 12-15. Each set of connected points represent measures along a row of electrodes on the surface array. Filled symbols show the masking produced by a surface electrode on the penetrating electrodes. PABI#1 shows large interference and the pattern of interference is similar across maskers. Fig 12 shows three masking curves for maskers at either end of the array and one in the middle. All produced similar masking patterns. There was no evidence of a peak in the masking function near the masker as would be expected. This result is consistent with the threshold measures from the surface array of this patient. Figure 1 shows thresholds as a function of electrode number along with a curve that represents a simple model of current flow. The model assumes that the current field from each electrode can be approximated by a simple inverse square law with a space constant of 1/mm. This simple model assumes that all activation occurs in the middle of the array near electrode 12. Threshold levels on all other electrodes simply reflect the amount of current necessary on those electrodes to produce a threshold level at the location of electrode 12. This implies that the surface electrode array in this patient is functioning as a single electrode, with all stimulation occurring in the middle of the array. The electrode interaction measures in Figure 12 are consistent with this interpretation – no selectivity is observed in the surface array. Interference could not be measured on the penetrating electrode because it had a limited dynamic range and the masked thresholds would have exceeded the 3 nC charge limit.

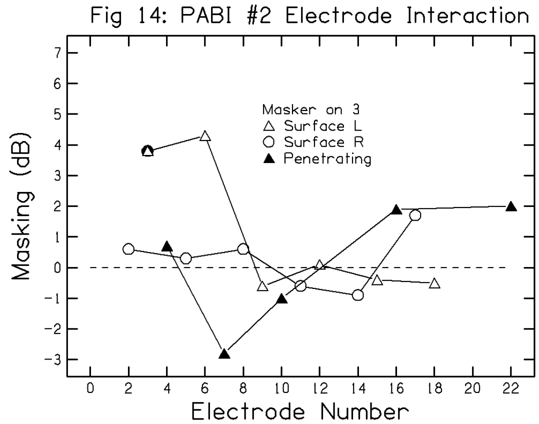
Figure 13 presents masking patterns for PABI#2 resulting from a masker on surface electrode 11 at 5 dB above threshold. The two curves with open symbols are from the linear arrays of surface electrodes along the two sides of the surface array. The filled symbols are from the penetrating electrodes.

Fig 13: PABI #2 Electrode Interaction



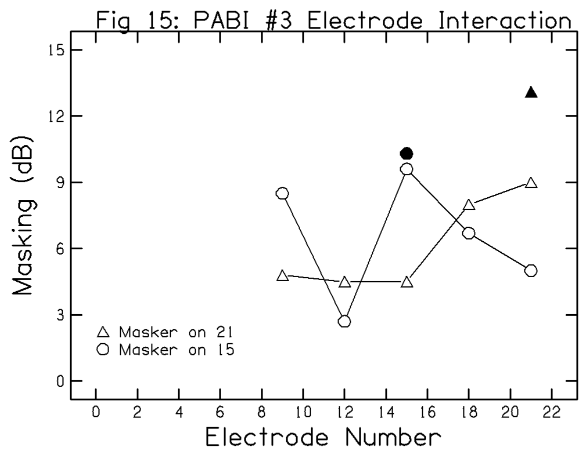
Observe that in this patient the masking shows modest selectivity - the amount of masking falls off as the probe electrode becomes more distant from the masker electrode. There is no clear difference in masking between one side of the array and the other. However, little masking was produced on the penetrating electrodes –

Fig 14: PABI #2 Electrode Interaction



maybe a slight amount on electrode 22. This suggests that the surface and penetrating electrodes in this patient are activation distinct neural populations. A second set of masking patterns was obtained from PABI#2 from a masker on one end of the surface array (electrode 3) at 7.5 dB above threshold. The results are presented in Fig 14. In this case a different pattern of masking was observed. Masking on the same side of the surface array was maximal at the masker location and at the next electrode, but was negligible for all other electrode. Little masking was observed at any location along the other side of the electrode array. Penetrating electrodes showed a mixed pattern of masking, with electrode 7 showing a release from masking while electrodes 16 and 22 showed a modest amount of masking. It is not clear if the negative masking observed is a reliable effect – additional measures are needed to confirm it. If confirmed it could indicate a possible inhibitory relation between surface and penetrating electrodes.

Figure 15 shows two electrode interference masking patterns for PABI#3. Maskers were placed on surface electrodes 15 and 21 and masking was measured for electrodes along the same side of the surface array. Masking could not be measured on penetrating electrodes because of the limited dynamic range imposed by the 3 nC limit. When the masker was on electrode 21 there was a reduction in masking with distance between the masker and probe electrodes, but there was still substantial masking at electrode 9, which was 3 mm away. The pattern obtained when the masker was on electrode 15 also shows a reduction in masking with masker-probe distance, with a reversal on electrode 9.

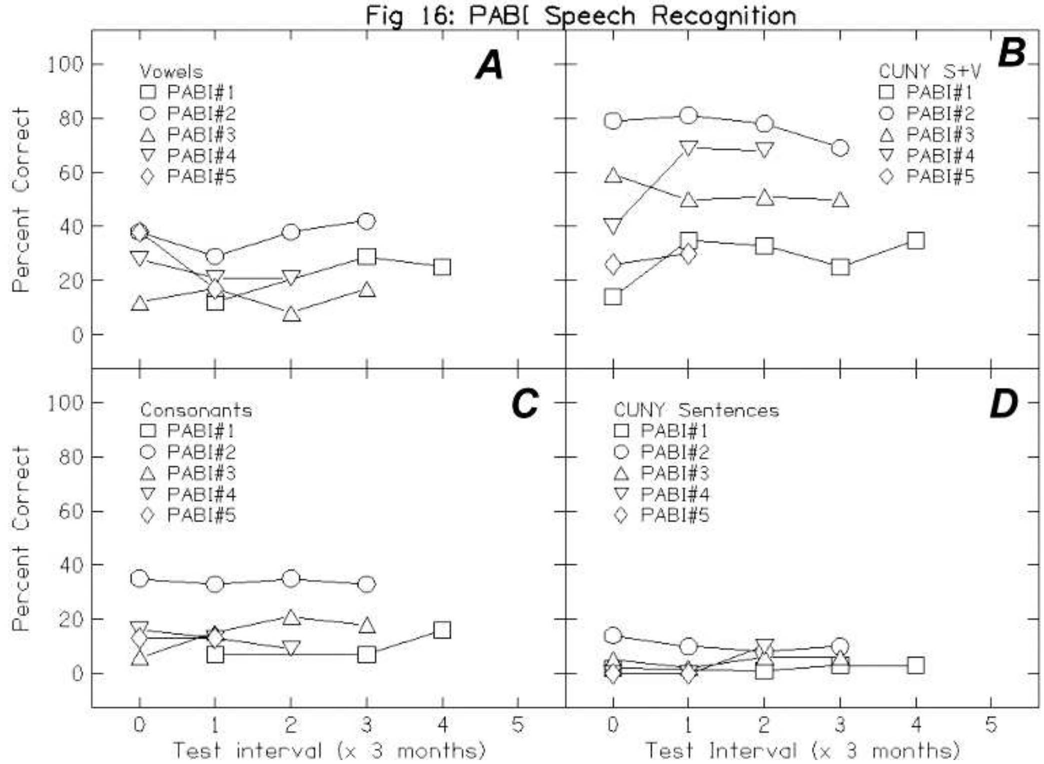


Overall the electrode selectivity measures present a mixed picture. For surface electrodes the selectivity appears to be poor to none (PABI#1). Penetrating electrodes can show little interference with surface electrode, some interference, or possibly even an enhancement from a masker on a surface electrode. This complex pattern might be explainable from the complex geometry of the surface electrodes relative to the penetrating electrodes. It might also result from neural propagation pathways, i.e. even if surface and penetrating electrodes stimulate distance neural populations the surface array might activate neurons that project to neurons near the penetrating electrodes and so produce secondary interference.

Speech results

Performance over time. PABI recipients are typically fitted with three speech processor maps for take-home use: a map that uses only surface electrodes, one that uses only penetrating electrodes (if possible) and a map that uses a combination of surface and penetrating electrodes. They are instructed to try each map to see if one is better suited for different listening conditions than the others. PABI patients 2 and 3, who have multiple functional penetrating electrodes, prefer the combination map for all listening conditions. PABI#1, who has only one penetrating electrode that produces audition, prefers the surface only map because the presence of the penetrating electrode in the map makes the overall quality “too squeaky”. In PABI patients 2 and 3, the map utilizing only penetrating electrodes is usually too soft (due to charge limit of 3 nC/phase) or sounds too mechanical. Through Cochlear Americas, we have petitioned the FDA to allow us to increase the maximum charge per phase for the penetrating electrodes to 8 nC. Recent animals studies conducted at HMRI have shown that this can be done safely, if the electrode surface area is increased to 5,000 μm^2, from the present 2,000 μm^2, and if the pulsing rate is limited to 250 Hz per electrode.

Fig 16: PABI Speech Recognition



In contrast to the penetrating electrodes, the patients report that the sound produced by the surface electrodes sound muffled. All three maps are tested at three-month intervals and the combination map is usually best in terms of overall performance. Figure 16 presents results over time from the 5 PABI patients using the best map, which is the combination map for PABI#2 and 3 and a surface only map for PABI#1, 4 and 5. Time interval zero indicates the results at initial hookup, while each other test point occurred at intervals of approximately 3 months. For speech materials there is no clear pattern of improvement over time, either on sound only tests (Figure 16 A,C,D) or on sound plus lip-reading tests (CUNY S+V, Figure 16 B).

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